Chapter 14

Ocular Rosacea

Aysun Sanal Dogan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66470

Abstract

Acne rosacea (AR) is a chronic cutaneous inflammatory disease of the midface. Ocular involvement occurs in 30–70% of patients. Although the incidence of this disease is seen highest between the ages of 30 and 50 years, it can also develop during childhood. The diagnosis depends on clinical findings such as meibomian gland dysfunction (MGD), conjunctival hyperemia, and corneal vascularization, and untreated cases can progress and lead to vision loss. Pathogenetic factors can be the altered the immune system, colonization of microorganisms, inflammation, abnormalities of sebaceous, and meibomian glands, environmental factors, and vascular dysregulation. Differential diagnosis from other ophthalmologic and dermatologic diseases is important. Management requires an interdisciplinary approach with a step-wise treatment algorithm. Patients should be informed about the chronic course of the disease and avoid the exacerbating factors. Caring about the lid hygiene and use of non-preserved artificial eye tears, topical ointments including antibiotics, anti-inflammatory agents are used when necessary. However, the mainstay of the therapy is the use of oral antibiotics for a long period. Surgical interventions may be needed in cases with a vision-threatening condition. During the long-term treatment period and disease course, the complications of medications should also be considered cautiously and patient should be followed up routinely.

Keywords: ocular rosacea, dry eye, meibomian gland, meibomian gland dysfunction, treatment

1. Introduction

Acne rosacea (AR) is the chronic inflammatory disease of skin typically involving the cheeks, nose, chin, and central forehead. The dermatological findings are transient or persistent erythema, papules, pustules, and telangiectasia. During the chronic course, these findings show exacerbations and remissions that may end up with progression. This dermatologic condition has been classified by National Rosacea Society into four subtypes based on the clinical fea-

tures: (1) erythematotelangiectatic rosacea, (2) papulopustular rosacea, (3) phymatous rosacea, and (4) ocular rosacea [1]. Flushing, chronic inflammation, and fibrosis are present in dermatologic course. The presence of one of the findings: flushing, non-transient erythema, plaque, dry appearance, edema, papules-pustules, and telangiectasia on the face with burning sensation, ocular manifestations, and phymatous changes is indicative of rosacea, and these symptoms are graded as mild, moderate, and severe [2]. Ocular manifestations are defined as one of the secondary criteria [1].

Under the circumstances of existing acne rosacea, the diagnosis of ocular rosacea (OR) is made by the presence of inflammation of the ocular surface, accompanying redness, burning, and itching symptoms of the eye. The diagnosis is confirmed by the presence of corneal infiltration with meibomian gland inflammation, and accompanying skin findings of rosacea [3].

2. Epidemiology

AR is usually seen between ages of 30 and 50 years [4, 5]. The prevalence is reported from 4 to 22% that is more frequent in fair-skinned people [5–8]. The OR starts to be detected approximately 10 years after the diagnosis of AR, with an increasing incidence between ages of 40 and 50 years [5]. The ocular involvement occurs in 58–72% and interestingly the ocular signs may precede in 20% of rosacea patients [9, 10]. Because of mild cutaneous manifestations, the ocular findings may be underestimated in children. Therefore, the diagnosis is delayed with more ocular complications. In a case series, it was shown that only two of six children with ocular rosacea demonstrated cutaneous rosacea findings [11].

Although AR affects women more than men, ocular involvement is to be seen in both sexes equally [5, 12]. There is a family history in 15–30% of cases [13, 14]. Hence, with a suspicion of family history, the children should be followed up closely and should be kept in mind that the condition tends to progress in adulthood [15].

3. Pathogenesis

Although AR has no proven cause, scientific studies showed that there is dysregulation of vascular, immunologic, and nervous systems [16, 17]. Ocular surface is the mainly affected area with OR. Ocular surface compromises cellular components of the palpebral and bulbar conjunctiva such as corneoscleral limbus, cornea, eyelid margins, eyelashes, and tear film [18].

3.1. Altered immune system

Altered immune system may be one of the factors. It was postulated that a type IV hypersensitivity reaction may be responsible for the conjunctival inflammation in OR in which the reactant is unknown [19, 20].

3.2. Colonization of microorganism

Demodex folliculorum is a saprophytic mite that is found in normal flora of the skin. There are studies demonstrating that the Demodex density increased in rosacea patients [21, 22].

Bacillus olenorium serum immunoreactivity was detected in ocular rosacea patients. Its proteins cause high immune reactions [22, 23].

Staphylococcus epidermidis and *Propionibacterium acnes* that are found commonly in lid flora are accused microorganisms for their production of high levels of bacterial lipases [24].

In a study, *Chlamydia pneumoniae* antigen was detected in 40% of skin biopsies patient with rosacea [25].

Moreover, *Helicobacter pylori* IgG antibodies were found in 81% of the acne rosacea patients with dyspepsia, but there is a debate whether this is a coincidence or not [26]. The proteins produced by these pathogens might be responsible for the some aspects of rosacea.

The increased amount of free fatty acids produced by meibomian glands causes tear film instability and irritates the ocular tissues [27]. This increase may be due to biochemical abnormality of the meibomian gland secretions or lipolytic exoenzymes of bacteria which degrade lipids into free fatty acids [28].

3.3. Inflammation

OR was found to be associated with the increased tear fluid levels of several inflammatory mediators such as interleukin-1 (IL-1) and gelatinase B activity [29]. Matrix metalloproteinases (MMP), interferon-alpha (IFN-α), and inflammatory cytokines seem to be an important component of pathophysiology [30].

The meibomian glands of rosacea patients cause keratinization of epithelial cells, end up with thickening of secretions, plugging of the orifices, and trapping of the secretions [31].

3.4. Environmental factors

Many rosacea patients are aware of some factors that exacerbate their symptoms. Although these triggering factors differ for each patient: alcohol, sunlight, wind, temperature extremes, hot, and spicy foods, vigorous exercise, hot baths, medications that dilate blood vessels, menopause, and emotional factors (stress, anger, and embarrassment) can also play role in the pathogenesis [32–34].

3.5. Genetics

Rosacea is associated with familial predisposition [35]. In a study conducted in twin pairs, rosacea contribution has been reported equally by genetic and environmental factors [36]. The genetic predisposition showed single nucleotide polymorphisms in HLA-DRA and BTNL2 genes that support the concept of a genetic component for rosacea [37].

3.6. Vascular dysregulation and neurologic system

There is vascular dilatation and telangiectatic vessels and increased blood flow, causing erythema, flushing, and neovascularization [5, 34, 38], which is probably under control of the sympathetic system [39].

4. Diagnosis

The diagnosis of both dermatological rosacea and ocular rosacea is clinical. There is no single-specific test—even skin biopsy—to confirm the diagnosis.

Ocular involvement is varied and non-specific. Most of the patients refer to ophthalmologist with dry eye symptoms (**Table 1**). No correlation exists between the severity of the ocular manifestations and that of the skin lesions. However, in patients with increased flushing, ocular rosacea prevalence is higher [40].

Although rosacea is uncommon in pediatric cases, it deserves attention due to undiagnosed ocular rosacea that is common with severe ocular complication [41]. History of triggering factors should be investigated and dermatologist consultation is required.

4.1. Clinical feature

Both eyes are usually affected simultaneously, but unilateral or sequential involvements can also occur.

The primary and the starter of the ocular involvement is the meibomian gland dysfunction (MGD) [42]. Ghanem et al. reported that the most common ocular signs in patients with rosacea from the ophthalmologic clinic were meibomian gland dysfunction (MGD) in 85.2%, lid margin telangiectasias in 53.4%, blepharitis in 44.3%, and interpalpebral hyperemia in 40.9%. Accordingly, patients from the dermatology clinic were reported to exhibit MGD in 27.3%, chalazion/hordeolum, lid margin telangiectasia in 18.2%, anterior blepharitis in 13.6%, and pinguecula in 13.6% [9] Vision loss is a rare but devastating complication [43]. OR has been graded as mild, moderate, and severe (**Table 2**) [2].

Ocular symptoms
– dryness sensations (burning and stinging, feeling of a having foreign body sensation in the eye)
– irritation
– itching
– redness
– sensitivity to light (photophobia)
– tearing
– red and swollen eyelids
– blurry or decreased vision

Table 1. Ocular symptoms of the ocular rosacea patient.

http://dx.doi.org/10.5772/66470

Grade	Involved areas	Signs and symptoms	Recommended treatment
Mild	Eyelid margin, meibomian gland	Mild itching and dry eye sensation Fine scaling and erythema of eyelid margins Mild conjunctival hyperemia	Topical treatment only
Moderate	Ocular surface	Moderate burning, tearing, foreign body sensation Eyelid margin irregularities, erythema and telangiectasia Prominent conjunctival hyperemia, ciliary injection Hordeolum and chalazion formation	Topical, systemic treatment
Severe	Corneal involvement and decreased vision	Pain, sensitivity to light, blurred vision Severe conjunctival inflammation, madarosis and trichiasis Corneal involvement	Topical, systemic, surgical treatment

Table 2. Grading of ocular rosacea [2].

4.2. Symptoms

Feeling of dryness, irritation symptoms with burning and stinging and feeling of having foreign body sensation in the eye are common. Blurry vision, redness, sensitivity to light (photophobia), tearing, itching, red, and swollen eyelids are the other encountered symptoms.

4.3. Signs

It is not rare that the symptoms of the patient are not proportional with the ocular findings. Reduced fluorescein tear breakup time, punctate staining on the cornea, and bulbar conjunctiva (**Figure 1**). Superficial punctate keratopathy (due to tear film instability), dry eye disease, blepharitis, styes, MGD, eyelid inflammation-collaretes, telangiectasis, conjunctival hyperemia, conjunctival scarring, punctate epithelial keratitis, corneal infiltrate/vascularization, corneal thinning, corneal astigmatism, corneal ulceration, phlyctenules, phlyctenular keratitis, limbal pannus, episcleritis, scleritis, corneal melting, and perforation, iritis, periorbital edema, recurrent chalazia, pannus, neovascularization, trichiasis (**Figures 1–5**) [43–46].

4.3.1. Eyelid

The lipid layer produced by meibomian glands stabilizes the tear film and prevents evaporation. Abnormality of this function is the primary cause of the blepharitis and evaporative-type dry eye. Dry eye can be detected by decreased tear breakup times. There is inflammation, dilatation, and occlusion of the meibomian glands [31]. With pressure to eyelid margins, there is hardness to express the secretion, and usually occluded by toothpaste-like material namely meibomana. Hordeolum and chalazion are the signs of focal inflamed obstructive MGD. In chronic course, there will be telangiectatic vessels around the orifices of the meibomian glands. At the end, the ducts are fully keratinized and disappears leading the meibomian gland dropout.

Figure 1. Ocular rosacea patient with irregular ocular margin, conjunctival hyperemia and trichiasis.

4.3.2. conjunctiva

Conjunctival hyperemia is the common finding. Hyperemia is mostly obvious in interpalpebral area. In 9% of OR, there is also conjunctival scarring [47].

4.3.3. cornea

Disease starts with inferior punctate epitheliopathy. Superficial vascularization of the peripheral cornea (especially triangular in shape and extending from inferior cornea) develops in

Figure 2. Ocular rosacea with sterile corneal infiltrate, lid telangiectasia, meibomian gland occlusion and foamy secretion.

http://dx.doi.org/10.5772/66470

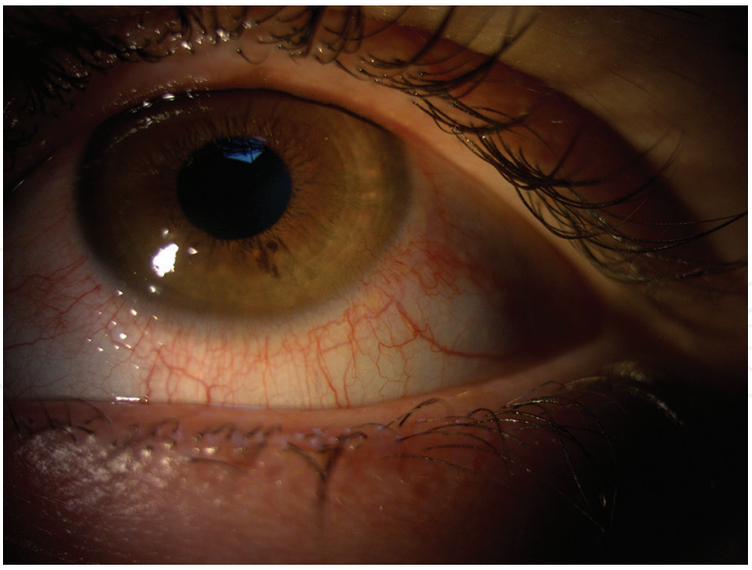

Figure 3. Bulbar interpalpebral conjunctival hyperemia with fine corneal vascularization.

untreated cases. In case of recurrent epithelium defects, one should be suspicious of OR also. Inflammatory episodes will end up with devastating problems, such as corneal scarring, thinning even perforation and sight threatening keratitis [48–51].

4.4. Ocular tests and imaging

Tests of evaporative dry eye are altered in OR. Tear osmolarity values, Ocular surface disease index (OSDI) questionnaire and corneal staining scores were significantly higher, and

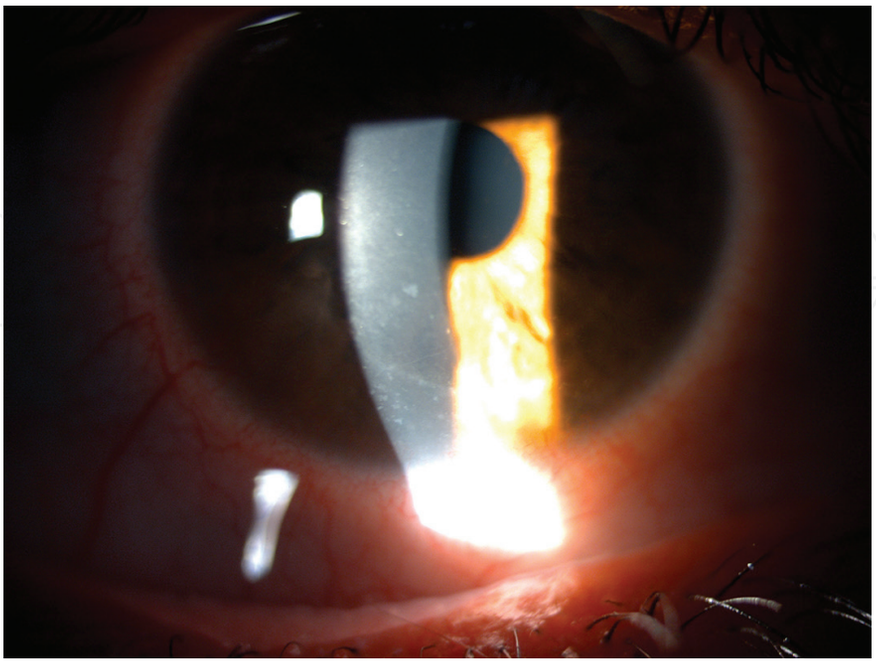

Figure 4. Ocular rosacea with severe dry eye symptoms and inferior punctate epitheliopathy.

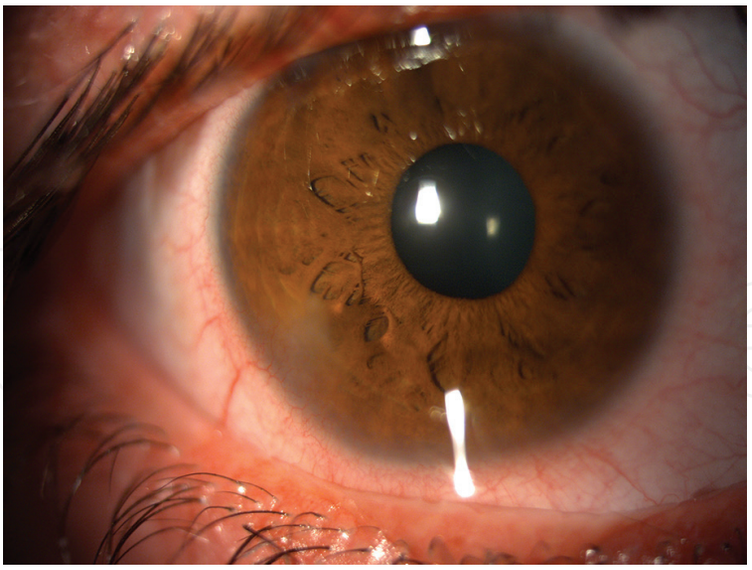

Figure 5. Corneal haze inferotemporally signifying healed corneal involvement of ocular rosacea.

Schirmer-I test and fluorescein tear breakup time were significantly lower, which all confirms tear hyperosmolarity and tear film dysfunction [52].

Dry eye in rosacea patients can also be diagnosed by tear meniscus measurement with optical coherence tomography (OCT) with considerable sensitivity and specificity [53]. Central corneal thickness, corneal hysteresis and corneal resistance factors were all significantly decreased in OR patients when compared to healthy controls [54]. Patients with OR show significant meibomian gland dropout which can be demonstrated by meibography (**Figure 6**)

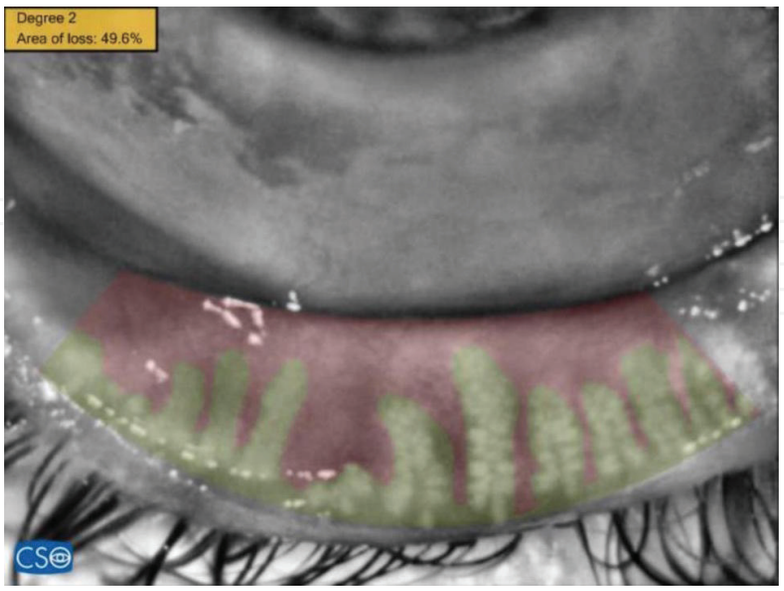

Figure 6. Ocular rosacea. Meibography, meibomian dropout.

[31, 42]. *In vivo* confocal microscopy findings revealed inflammatory changes of ocular surface and even Demodex infestations on eyelids [55, 56].

5. Differential diagnosis

5.1. From dermatological diseases

In patients with suspicion of OR, if facial dermatologic inflammatory changes exist, clinician would be aware of three main differential diagnosis [57]. These are as follows:

Acne vulgaris: The presence of comedones—which does not exist in rosacea—in young patients direct the clinician to diagnosis of acne vulgaris.

Seborrheic dermatitis: In seborrheic dermatitis, facial erythema is accompanied by yellowish scaling and prominent dandruff.

Perioral dermatitis: There is perioral involvement without flushing or telangiectasia.

5.2. From ophthalmological diseases

Ocular findings must be differentiated from the other causes of dry eye.

Corneal involvements must be differentiated from herpetic or bacterial keratitis and recurrent epithelial defects [48, 58, 59].

All forms of conjunctivitis are in differential diagnosis. Due to chronic course and leading to conjunctival scarring, chlamydial conjunctivitis deserves attention.

In severe OR, which ends up with inferior thinning and irregular astigmatism, it may resemble to keratoconus [51].

6. Management

For an effective therapeutic strategy, an interdisciplinary collaboration is needed between ophthalmologist and dermatologist. The stepwise approach is recommended.

- Inform patient about the chronic nature of their disease and requirement for regular follow-up.
- Avoid triggering and exacerbating factors. It might be advised to keep a daily diary to figure out triggering factors.
- Avoid wearing contact lenses and eye makeup when the symptoms are exaggerated.
- Lid hygiene: Hot compressing and MG expressions by mechanical massage to lids, lid hygiene cleaning solutions, eyelid scrubs massage to the tarsal plate [60]. This is the main approach and must be recommended to all OR patients

- Lubricants: Lubricants are used to decrease inflammatory mediators, and to provide symptomatic relief. Non-preserved artificial tears are recommended with a patient-individualized dosage [61]. The initial high dosages might be tapered gradually. OR is usually mild and responds well to lid hygiene and lubricants, but must be advised to do regularly to avoid exacerbations of symptoms.

- Topical antibiotics: Azithromycin 1.5% eye drops are effective for MGD treatment even with phlyctenular keratoconjunctivitis complicating OR [62, 63]. It has an anti-inflammatory effect as well as an antimicrobial effect. Topical antibiotic ointments (fucidic acid and metronidazole gel applied to lid margins), especially in the nighttime, are also effective to restore the flora.

- Mainstay of the treatment is the use of systemic antibiotics. Due to relapses, maintenance treatment may be 6 months. Low doses with longer duration of the antibiotic usage must be preferred to benefit from the anti-inflammatory effect without inducing resistance and other side effects.

  - Systemic tetracycline/doxycycline/minocycline shows the therapeutic effects by decreasing lid flora, inhibiting collagenase activity which prevents corneal thinning, inhibiting inflammatory mediators (i.e. MMP), decreasing concentration of free fatty acids [64–66].

  - Clarithromycin are also effective to *H. pylori* [67].

  - Metronidazole has anti-inflammatory, anti-microbic, anti-parasitic, and immunosuppressive effects [68].

  - Azithromycin 3 times per week for 4 weeks [69].

  - Erythromycin is appropriate for children <8 years old to avoid the untoward effects of tetracycline [70].

- Topical anti-inflammatory agents: Topical corticosteroids suppress the exacerbation episodes and are effective in prevention of the recurrent corneal erosions when used in combination with systemic doxycycline [71]. The application would be tapered and stopped after the symptomatic relief. Topical steroids should be used cautiously, minimal dose with minimal duration, under the supervision of the ophthalmologist. Instead of steroids, topical cyclosporine (with 0.05% concentration) might be the choice for a longer period of treatment [72].

- Dietary intervention with omega-3 fatty acids for 6 months is effective in decreasing the dry eye symptoms and signs in ocular rosacea [73].

- Surgical: Intraductal meibomian gland probing is shown to be a promising technique to improve dry eye symptoms related with OR [74]. Epilation of trichiatic lashes will eliminate the mechanical insult to ocular surface.

In cases of severe corneal involvement, surgical options are indicated [49]. Progressive epitheliopathy unresponsive to topical treatment with hazy epithelium extending centrally,

indicating limbal stem cell insufficiency, is treated with limbal stem cell transplantation [75]. Thinning of the cornea and threatening perforation are treated with conjunctival flaps or amniotic membranes [43]. Little corneal perforations may benefit from cyanoacrylate glues. Minority people with untreated or resistant to treatment may need keratoplasty at the end of long-term OR [49].

Rosacea naturally waxes and wanes. However, because the damage from rosacea can be progressive, the long-lasting use of therapy has advantages. Due to the lack of prospective controlled studies, the optimum modality and duration for treatment and prevention of OR recurrence remain unclear. The duration of the treatment depends on the ophthalmologist's decision and the severity of the ocular involvement. There is a consensus to give treatment for several months, and tapering the doses within follow-ups.

7. Complications

Long-standing OR will end up with irregular eyelid margins and misdirected eyelashes (trichiasis). Untreated corneal involvement will lead to vision loss.

The long-term use of topical steroids may cause increased intraocular pressure, cataract formation, corneal thinning, and exacerbation of underlying herpes. Chronic use of systemic antibiotics makes necessary to control the hepatic functions.

Although it is recommended to use low dose with a long duration, clinician should be cautious about the potential side effects of oral tetracycline as gastrointestinal discomfort, vaginal yeast infections, photosensitivity, and decreased effectiveness of oral contraceptives. It is not appropriate for the children <8 years old, because of its accumulation in bone, color changes in teeth, and interfering enamel development [76].

Oral isotretinoin, which has both anti-inflammatory and immunomodulatory properties, has been used as a treatment for severe rosacea, particularly phymatous presentation by dermatologists [77]. In these cases, routine ophthalmologic follow-up should be recommended since the retinoids may cause blepharoconjunctivitis, worsening telangiectasias and may lead to severe keratitis [78].

8. Conclusion

Rosacea, mainly being a dermatological disease, may show ocular manifestations that sometimes may have severe consequences. The diagnosis mainly depends on the clinical findings and suspicion of the clinician. The evaluation and management should be performed by a collaborative approach by both dermatologist and ophthalmologist. The management should have a stepwise structure. The complications of both the disease and the treatment should be considered during the disease course.

Author details

Aysun Sanal Dogan

Address all correspondence to: asanaldogan@gmail.com

Ophthalmology Department, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

References

[1] Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. J Am Acad Dermatol. 2002;**46**:584–587. DOİ:10.1067/mjd.2002.120625.

[2] Wilkin J, Dahl M, Detmar M, Drake L, Liang MH, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. J Am Acad Dermatol. 2004;**50**:907–912. DOİ:10.1016/j.jaad.2004.01.048.

[3] Vieira AC, Mannis MJ. Ocular rosacea: common and commonly missed. J Am Acad Dermatol. 2013;**69**:36–41. DOI: 10.1016/j.jaad.2013.04.042.

[4] Sobye P. Aetiology and pathogenesis of rosacea. Acta Derm Venereol. 1950;**30**:137–158.

[5] Berg M, Lidén S. An epidemiological study of rosacea. Acta Derm Venereol (Stockh). 1989;**69**:419–423.

[6] Halder RM, Brooks HL, Callendar VD. Acne in ethnic skin. Dermatol Clin. 2003;**21**:609–615. DOI: 10.1016/S0733-8635(03)00082-2.

[7] Tan J, Schöfer H, Araviiskaia E, Audibert F, Kerrouche N, et al; RISE study group. Prevalence of rosacea in the general population of Germany and Russia—the RISE study. J Eur Acad Dermatol Venereol. 2016;**30**:428–434. DOI: 10.1111/jdv.13556.

[8] Abram K, Silm H, Oona M. Prevalence of rosacea in an Estonian working population using a standard classification. Acta Derm Venereol. 2010;**90**:269–273. DOI: 10.2340/00015555-0856.

[9] Ghanem VC, Mehra N, Wong S, Mannis MJ. The prevalence of ocular signs in acne rosacea: comparing patients from ophthalmology and dermatology clinics. Cornea. 2003;**22**:230–233. DOI: 10.1097/00003226-200304000-00009.

[10] Bakar O, Demircay Z, Toker E, Cakir S. Ocular signs, symptoms and tear function tests of papulopustular rosacea patients receiving azithromycin. J Eur Acad Dermatol Venereol. 2009;**23**:544–549. DOI: 10.1111/j.1468-3083.2009.03132.x.

[11] Nazir SA, Murphy S, Siatkowski RM, et al. Ocular rosacea in childhood. Am J Ophthalmol. 2004;**137**:138–144. DOI: 10.1016/S0002-9394(03)00890-0.

[12] Spoendlin J, Voegel JJ, Jick SS, Meier CR. A study on the epidemiology of rosacea in the UK. Br J Dermatol. 2012;**167**:598–605. DOI: 10.1111/j.1365-2133.2012.11037.x.

[13] Donaldson KE, Karp CL, Dunbar MT. Evaluation and treatment of children with ocular rosacea. Cornea. 2007;**26**:42–46. DOI: 10.1097/ICO.0b013e31802e3a54.

[14] Rebora A. The red face: rosacea. Clin Dermatol. 1993;**11**:225–234.

[15] Kroshinsky D, Glick SA. Pediatric rosacea. Dermatol Ther 2006; **19**:196–201. DOI: 10.1016/0738-081X(93)90058-K.

[16] Webster GF. Rosacea. Med Clin North Am. 2009;**93**:1183–1194. DOI: 10.1016/j.mcna.2009.08.007.

[17] Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. J Am Acad Dermatol. 2013;**69**:15–26. DOI: 10.1016/j.jaad.2013.04.045.

[18] Yañez-Soto B, Mannis MJ, Schwab IR, Li JY, Leonard BC, et al. Interfacial phenomena and the ocular surface. Ocul Surf. 2014;**12**:178–201. DOI: 10.1016/j.jtos.2014.01.004.

[19] Hoang-Xuan T, Rodriquez A, Zaltas MM, Rice BA, Foster CS. Ocular rosacea. A histologic and immunopathologic study. Ophthalmology 1990;**97**:1468–1475. DOI: 10.1016/S0161-6420(90)32403-X.

[20] Faraj HG, Hoang-Xuan T. Chronic cicatrizing conjunctivitis. Curr Opin Ophthalmol. 2001;**12**:250–257. DOI: 10.1097/00055735-200108000-00003.

[21] Georgala S, Katoulis AC, Kylafis GD, Koumantaki-Mathioudaki E, Georgala C, Aroni K. Increased density of Demodex folliculorum and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. J Eur Acad Dermatol Venereol 2001;**15**:441–444. DOI: 10.1046/j.1468-3083.2001.00331.x.

[22] O'Reilly N, Gallagher C, Reddy Katikireddy K, Clynes M, O'Sullivan F, Kavanagh K. Demodex-associated Bacillus proteins induce an aberrant wound healing response in a corneal epithelial cell line: possible implications for corneal ulcer formation in ocular rosacea. Invest Ophthalmol Vis Sci. 2012;**53**:3250–3259. DOI: 10.1167/iovs.11-9295.

[23] O'Reilly N, Menezes N, Kavanagh K. Positive correlation between serum immunoreactivity to Demodex-associated Bacillus proteins and erythematotelangiectatic rosacea. Br J Dermatol. 2012;**167**:1032–1036. DOI: 10.1111/j.1365-2133.2012.11114.x.

[24] Dahl MV,,Ross AJ, Schlievert PM. Temperature regulates bacterial protein production: possible role in rosacea. J Am Acad Dermatol. 2004; **50**:266–272.

[25] Fernandez-Obregon A, Patton DL. The role of Chlamydia pneumoniae in the etiology of acne rosacea: response to the use of oral azithromycin. Cutis. 2007;**79**:163–167.

[26] Argenziano G, Donnarumma G, Iovene MR, Arnese P, Baldassarre MA, et al. Incidence of anti-Helicobacter pylori and anti-CagA antibodies in rosacea patients. Int J Dermatol. 2003;**42**:601–604.

[27] McCulley JP, Dougherty JM, Deneau DG. Classification of chronic blepharitis. Ophthalmology. 1982 Oct;**89**:1173–1180.

[28] Arita R, Mori N, Shirakawa R, Asai K, Imanaka T, et al. Meibum color and free fatty acid composition in patients with meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2015;**56**:4403–4412. DOI: 10.1167/iovs.14-16254.

[29] Afonso AA, Sobrin L, Monroy DC, Selzer M, Lokeshwar B, et al. Tear fluid gelatinase B activity correlates with IL-1alpha concentration and fluorescein clearance in ocular rosacea. Invest Ophthalmol Vis Sci. 1999;**40**:2506–2512.

[30] Barton K, Monroy DC, Nava A, Pflugfelder SC. Inflammatory cytokines in the tears of patients with ocular rosacea. Ophthalmology. 1997;**104**:1868–1874. DOI: 10.1016/S0161-6420(97)30014-1.

[31] Machalińska A, Zakrzewska A, Markowska A, Safranow K, Wiszniewska B, et al. Morphological and functional evaluation of meibomian gland dysfunction in rosacea patients. Curr Eye Res. 2015;**7**:1–6. DOI: 10.3109/02713683.2015.1088953.

[32] Goldgar C, Keahey DJ, Houchins J. Treatment options for acne rosacea. Am Fam Physician. 2009;**80**:461–468.

[33] Odom R, Dahl M, Dover J, Draelos Z, Drake L, et al. Standard management options for rosacea, Part 1: overview and broad spectrum of care. Cutis. 2009;**84**:43–47.

[34] Odom R, Dahl M, Dover J, Draelos Z, Drake L, et al. Standard management options for rosacea, Part 2: options according to subtype. Cutis. 2009;**84**:97–104.

[35] Abram K, Silm H, Maaroos HI, Oona M. Risk factors associated with rosacea. J Eur Acad Dermatol Venereol. 2010;**24**:565–571. DOI: 10.1111/j.1468-3083.2009.03472.x.

[36] Aldrich N, Gerstenblith M, Fu P, Tuttle MS, Varma P, et al. Genetic vs. environmental factors that correlate with rosacea: a cohort-based survey of twins. JAMA Dermatol. 2015;**151**:1213–1219. DOI: 10.1001/jamadermatol.2015.2230.

[37] Chang AL, Raber I, Xu J, Li R, Spitale R, et al. Assessment of the genetic basis of rosacea by genome-wide association study. J Invest Dermatol. 2015;**135**:1548–1555. DOI: 10.1038/jid.2015.53.

[38] Del Rosso JQ. Management of facial erythema of rosacea: what is the role of topical α-adrenergic receptor agonist therapy? J Am Acad Dermatol. 2013;**69**:44–56. DOI: 10.1016/j.jaad.2013.06.009.

[39] Metzler-Wilson K, Toma K, Sammons DL, Mann S, Jurovcik AJ, et al. Augmented supra-orbital skin sympathetic nerve activity responses to symptom trigger events in rosacea patients. J Neurophysiol. 2015;**114**:1530–1537. DOI: 10.1152/jn.00458.2015.

[40] Starr PA, Macdonald A. Oculocutaneous aspects of rosacea. Proc R Soc Med. 1969; **62**:9–11.

[41] Lacz NL, Schwartz RA. Rosacea in the pediatric population. Cutis. 2004;**74**:99–103.

[42] Palamar M, Degirmenci C, Ertam I, Yagci A. Evaluation of dry eye and meibomian gland dysfunction with meibography in patients with rosacea. Cornea. 2015;**34**:497–499. DOI: 10.1097/ICO.0000000000000393.

[43] López-Valverde G, Garcia-Martin E, Larrosa-Povés JM, Polo-Llorens V, Pablo-Júlvez LE. Therapeutical management for ocular rosacea. Case Rep Ophthalmol. 2016;**7**:237–242. DOI: 10.1159/000446104.

[44] Michel JL, Cabibel F. Frequency, severity and treatment of ocular rosacea during cutaneous rosacea. Ann Dermatol Venerol. 2003;**130**:20–24. DOI: AD-01-2003-130-1-0151-9638-101019-ART5.

[45] Chen DM, Crosby DL. Periorbital edema as an initial presentation of rosacea. J Am Acad Dermatol. 1997;**37**:346–348. DOI: 10.1016/S0190-9622(97)80389-1.

[46] Weisenthal RW, Afshari NA, Bouchard CS, Colby KA, Rootman DS, Tu EY, de Freitas D. Chapter 3: Clinical approach to ocular surface disorders. In: Cantor LB,Rapuano CJ, Cioffi GA, editors. Basic and Clinical Science Course, Section 8 (2014-2015). External Disease and Cornea. San Fransisco, CA; American Academy of Ophthalmology , 2014. P.37-81.

[47] Akpek E, Merchant A, Pinar V, Foster CS. Ocular rosacea: patient characteristics and follow-up. Ophthalmology. 1997;**104**:1863–1867. DOI: 10.1016/S0161-6420(97)30015-3.

[48] Jain V, Shome D, Natarajan S. Pseudodendritic keratitis in ocular rosacea causing a diagnostic dilemma. Indian J Ophthalmol. 2007;**55**:480–481. DOI: 10.4103/0301-4738.36493.

[49] Gracner B, Pahor D, Gracner T. Repair of an extensive corneoscleral perforation in a case of ocular rosacea with a keratoplasty. Klin Monbl Augenheilkd. 2006;**223**:841–843. DOI: 10.1055/s-2006-926720.

[50] Awais M, Anwar MI, Iftikhar R, Iqbal Z, Shehzad N, et al. Rosacea—the ophthalmic perspective. Cutan Ocul Toxicol. 2015;**34**:161–166. DOİ: 10.3109/15569527.2014.930749.

[51] Dursun D1, Piniella AM, Pflugfelder SC. Pseudokeratoconus caused by rosacea. Invest Ophthalmol Vis Sci. 1999;**40**:2506–2512. DOI: 10.1097/00003226-200108000-00024.

[52] Karaman Erdur S, Eliacik M, Kocabora MS, Balevi A, Demirci G, et al. Tear osmolarity and tear film parameters in patients with ocular rosacea. Eye Contact Lens. 2015;**27**:1–3. DOI: 10.1097/ICL.0000000000000211.

[53] Eroglu FC, Karalezli A, Dursun R. Is optical coherence tomography an effective device for evaluation of tear film meniscus in patients with acne rosacea? Eye (Lond). 2016;**30**:545–552. DOI: 10.1038/eye.2015.277.

[54] Yildirim Y, Olcucu O, Agca A, Karakucuk Y, Alagoz N, et al. Topographic and biomechanical evaluation of corneas in patients with ocular rosacea. Cornea. 2015;**34**:313–317. DOİ: 10.1097/ICO.0000000000000350.

[55] Leduc C, Dupas B, Ott-Benoist AC, Baudouin C. Advantages of the in vivo HRT2 corneal confocal microscope for investigation of the ocular surface epithelia. J **F**r Ophthalmol. 2004;**27**:978–986. DOI: JFO-11-2004-27-9-C1-0003-4266-101019-ART02.

[56] Randon M, Liang H, El Hamdaoui M, Tahiri R, Batellier L, et al. In vivo confocal microscopy as a novel and reliable tool for the diagnosis of Demodex eyelid infestation. Br J Ophthalmol. 2015;**99**:336–341. DOİ: 10.1136/bjophthalmol-2014-305671.

[57] Culp B, Scheinfeld N. Rosacea: a review. P T. 2009;**34**:38–45.

[58] Ramamurthi S, Rahman MQ, Dutton GN, Ramaesh K. Pathogenesis, clinical features and management of recurrent corneal erosions. Eye (Lond). 2006;**20**:635–644. DOI: 10.1038/sj.eye.6702005.

[59] Derrar R, Daoudi R. Confusion between rosacea and bacterial keratitis. Pan Afr Med J. 2014;**18**:81. DOI: 10.11604/pamj.2014.18.81.4390.

[60] Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011;**52**:2050–2064. DOI: 10.1167/iovs.10-6997g.

[61] Auw-Haedrich C, Reinhard T. Chronic blepharitis. Pathogenesis, clinical features, and therapy. Ophthalmologe. 2007;**104**:817–826. DOI: 10.1007/s00347-007-1608-8.

[62] Doan S, Gabison E, Chiambaretta F, Touati M, Cochereau I. Efficacy of azithromycin 1.5% eye drops in childhood ocular rosacea with phlyctenular blepharokeratoconjunctivitis. J Ophthalmic Inflamm Infect. 2013;**3**:38. DOI: 10.1186/1869-5760-3-38.

[63] Murphy BS, Sundareshan V, Cory TJ, Hayes D Jr, Anstead MI, et al. Azithromycin alters macrophage phenotype. J Antimicrob Chemother. 2008;**61**:554–560. DOI: 10.1093/jac/dkn007.

[64] Del Rosso JQ, Thiboutot D, Gallo R, Webster G, Tanghetti E, et al. Consensus recommendations from the American Acne and Rosacea Society on the management of rosacea. Part 3: a status report on systemic therapies. Cutis. 2014;**93**:18–28.

[65] Sobolewska B, Doycheva D, Deuter C, Pfeffer I, Schaller M, et al. Treatment of ocular rosacea with once-daily low-dose doxycycline. Cornea. 2014;**33**:257–260.

[66] Jackson JM, Kircik LH, Lorenz DJ. Efficacy of extended-release 45 mg oral minocycline and extended-release 45 mg oral minocycline plus 15% azelaic acid in the treatment of acne rosacea. J Drugs Dermatol. 2013;**12**:292–298.

[67] Rebora A. The management of rosacea. Am J Clin Dermatol. 2002;**3**:489–496. DOI: 10.2165/00128071-200203070-00005

[68] Pye RJ, Burton JL. Treatment of rosacea by metronidazole. Lancet. 1976;**1**:1211–1212.

[69] Bakar O, Demirçay Z, Gürbüz O. Therapeutic potential of azithromycin in rosacea. Int J Dermatol. 2004;**43**:151–154. DOI: 10.1111/j.1365-4632.2004.01958.x.

[70] Miguel AI, Salgado MB, Lisboa MS, Henriques F, Paiva MC et al. Pediatric ocular rosacea: 2 cases. Eur J Ophthalmol. 2012;**22**:664–666. DOI: 10.5301/ejo.5000103.

[71] Dursun D, Kim MC, Solomon A, Pflugfelder SC. Treatment of recalcitrant recurrent corneal erosions with inhibitors of matrix metalloproteinase-9, doxycycline and corticosteroids. Am J Ophthalmol. 2001;**132**:8–13. DOI: 10.1016/S0002-9394(01)00913-8.

[72] Arman A, Demirseren DD, Takmaz T. Treatment of ocular rosacea: comparative study of topical cyclosporine and oral doxycycline. Int J Ophthalmol. 2015;**8**:544–549. DOI: 10.3980/j.issn.2222-3959.2015.03.19.

[73] Bhargava R, Chandra M, Bansal U, Singh D, Ranjan S, et al. Randomized controlled trial of omega 3 fatty acids in rosacea patients with dry eye symptoms. Curr Eye Res. 2016;**6**:1–7. DOI: 10.3109/02713683.2015.1122810.

[74] Wladis EJ. Intraductal meibomian gland probing in the management of ocular rosacea. Ophthal Plast Reconstr Surg. 2012;**28**:416–418. DOI: 10.1097/IOP.0b013e3182627ebc.

[75] Kim BY, Riaz KM, Bakhtiari P, Chan CC, Welder JD, et al. Medically reversible limbal stem cell disease: clinical features and management strategies. Ophthalmology. 2014;**121**:2053–2058. DOI: 10.1016/j.ophtha.2014.04.025.

[76] Gruber GG, Callen JP. Systemic complications of commonly used dermatologic drugs. Cutis. 1978;**21**:825–829.

[77] Park H, Del Rosso JQ. Use of oral isotretinoin in the management of rosacea. J Clin Aesthet Dermatol. 2011;**4**:54–61.

[78] Aragona P, Cannavò SP, Borgia F, Guarneri F. Utility of studying the ocular surface in patients with acne vulgaris treated with oral isotretinoin: a randomized controlled trial. Br J Dermatol. 2005;**152**:576–578. DOI: 10.1111/j.1365-2133.2005.06389.x.

IntechOpen